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Detection of Memory Deficits Secondary to Epilepsy

by

Gregg Shanks ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

Centre for Neuroscience

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University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *Detecting Memory Deficits Secondary to Epilepsy* submitted by Gregg Shanks in partial fulfillment of the requirements of the degree of Master of Science.

DEDICATION

This project is dedicated to the loving memory of Ms. Elaine Rhodes, and to all other parents of children with epilepsy who see the real person behind the disorder.

ABSTRACT

The present study endeavored to examine the effectiveness of a newly developed memory test for the identification of epilepsy in participants and also the isolation and characterization of different epilepsy disorders. This protocol focused strictly on working memory. The test was found to successfully identify participants with epilepsy from those without, with epilepsy participants performing worse than controls. Participants with epilepsy activity in both hemispheres were found to generally perform worse than participants with activity limited to either the left or right hemisphere, for both verbal and nonverbal cognitive load conditions. Participants with activity limited to the right or left hemisphere could not be differentiated statistically. Possible reasons for poorer performance by participants with epilepsy activity in both hemispheres for both verbal and visual cognitive load conditions are discussed.

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LIST OF COMMON ABBREVIATIONS

ACC……………………………………………………………..Accuracy
CVLT……………………………………California Verbal Learning Test
EEG……………………………………………………Electroencephalogram
RAVLT………………………………Rey Auditory Verbal Learning Test
RCFT………………………………………….Rey Complex Figure Test
RT……………………………………………………………Reaction Time
SRT…………………………………………..…Subtracted Reaction Time
TCI…………………………………….Temporary Cognitive Impairment
TLE…………………………………………….Temporal Lobe Epilepsy
WAIS-R……..………………Wechsler Adult Intelligence Scale- Revised
WMS-R…………………………………Wechsler Memory Scale-Revised
WPT…………………………………….……Wonderlic Personnel Test
WRMT…….……………………..Warrington Recognition Memory Test

INTRODUCTION

A number of neuropsychological tests have been used to expose differences between epileptic patients and controls, and right and left focal epilepsy. These tests, however, have had mixed success in characterizing the existence and location of epileptiform activity. Typically such tests are organized into batteries, but results suggest that some batteries are not equal to the intended task [18; 27; 40]. Consequently, establishing a cognitive profile that specifically identifies epileptic disorders compared to controls and other disorders would be an important clinical advance. Similarly, successful identification of the different kinds of epilepsy based on such a profile would assist in the treatment of newly diagnosed epilepsy patients, as it could indicate the possibility of corrective surgery for the patient. Several of the tests currently used are not sensitive enough to pinpoint specific cognitive deficits secondary to epilepsy [19] nor are they used consistently enough to establish their efficacy [63]. For example, Cochrane et al. [19] found of the 87 tests reviewed, only 20 were found to show statistically significant cognitive effects in epileptic patients, and that only 13 of the tests they encountered in their review were used more than four times in antiepileptic drug testing. This present study endeavored to examine the effectiveness of a newly developed memory test.

There were two objectives for this study. The first was to assess the usefulness of the memory test in the identification of epilepsy in participants. The second objective was the isolation and characterization of different kinds of epilepsy disorders within groups of participants with epilepsy. This experimental protocol focused strictly on working memory as this process has been implicated in the assessment of epilepsy deficits [18] and because there is indication that memory activation may decrease temporal lobe

seizure threshold [37] suggesting that memory tasks have a close relationship with seizure activity. It is believed that memory testing is the best indicator of cognitive impairments associated with epilepsy.

General cognitive impairments have been studied in persons with epilepsy [6; 20; 29; 34; 53; 62; 67], and are demonstrated by categorically poorer performance on standardized tests of cognitive abilities. Comparatively little effort has been devoted to the characterization of the *specific* cognitive deficits of epilepsy between seizures [10; 30; 32]. However, it is known that epilepsy not only causes cognitive effects during clinical seizures and immediately after, but can also cause impairment due to epileptiform activity without clinically recognized seizures [10; 11; 33; 61]. The effects of this epileptiform activity are clinically recognized as transient cognitive impairment (TCI) or interictal impairment [9; 43], because it causes subtle, higher order processing deficits. Unfortunately, the higher order cognitive deficits that compose TCI, such as memory, attention, and language, are difficult to isolate using current neuropsychological batteries [10; 27; 43; 61; 63], but systematic examination of these processes would provide a clinically relevant understanding of the profile associated with epilepsy [39; 43; 52].

One of the most relevant factors to cognitive impairments secondary to epilepsy is the age of onset of epilepsy, where better performance is seen with later age of onset [13; 20; 26; 28; 35; 43]. But equally important is the type of epilepsy, as differences in testing performance has been shown to identify particular forms of epilepsy [35; 38; 41; 42; 63; 64].

Several studies have reported testing that can differentiate between a right or left epilepsy focus [4; 7; 34; 41; 64; 65; 66] to the extent that performance on specific tests

differ as a function of focus location [44; 45]. For example, language based testing has been shown to identify a typical left focus patient [2; 20; 46; 55; 58; 64; 65]. Conversely, right focus patients have shown impaired performance on testing of visual memory and visual perception [3; 46; 47; 48]. Nevertheless, a more thorough examination of the tests commonly used with epilepsy patients reveals a great deal of controversy and conflicting findings as to the effectiveness of certain neuropsychological tools. One of the most difficult areas to distinguish between epileptics and controls, or the different kinds of epilepsy, has been shown to be memory testing.

MEMORY TESTS CURRENTLY USED IN THE DIAGNOSIS OF EPILEPSY

There are mixed conclusions for the ability of various standardized tests of memory to diagnose epilepsy. Use of the revised Wechsler Memory Scale [WMS-R; 69] has shown poorer memory in epilepsy participants compared to controls [21; 53], yet other investigations revealed no difference between participants with epilepsy and controls [12].The California Verbal Learning Test [CVLT; 22] was found to differentiate control participants from those with mesial temporal lobe epilepsy (TLE) or mesial TLE with left temporal malformation [56], and the Selective Reminding Procedure [16] was found to differentiate controls from left temporal and extratemporal patients[34]. The Benton Visual Retention Test [5] appears unable to differentiate generalized epilepsy patients from left TLE, right TLE, or controls [58]. However, this test did coincide with seizure initiation in patients with prior seizure activity [37], suggesting that the processing it requires may map onto seizure activity at some level. The Rey Complex Figure Test [RCFT; 54] was found to differentiate between epileptics and controls, but not between severity of epilepsy conditions [46]. The Digit Span test was also found to coincide with seizure onset [37], but no significant difference between epilepsy and controls has also been found [8]. Hence the ability of certain memory tests to distinguish people with epilepsy from controls is justifiably in question. The literature on neuropsychological testing to identify the location of epilepsy activity is perhaps even more controversial.

The RCFT for episodic and visual memory can differentiate between left and right TLE participants [46], but not between mesial temporal schlerosis epilepsy participants and those with additional left temporal developmental malformation [56]. Moreover, other researchers have found that the RCFT was unable to differentiate between right

temporal, left temporal, or generalized epilepsy [58]. The Rey Auditory Verbal Learning Test [RAVLT; 54] is incapable of differentiating right or left temporal lobe epilepsy, regardless of prefrontal metabolic asymmetry [46], yet the German version of this test (VLMT), coincided with seizure occurrence in patients with left and right temporal lobe epilepsy during neuropsychological examination [37], suggesting an effect on seizure threshold. The Corsi Block Tapping Test [59] for visual spatial memory differentiates between patients with frontal lobe epilepsy compared to TLE [38], but not between right and left TLE patients scheduled for surgical removal [36; 46].

Use of the revised Wechsler Memory Scale is extremely common in neuropsychological evaluation of people with epilepsy, yet many results suggest that its usefulness is questionable. Participants with more motor seizures performed worse than those with fewer motor seizures [23] on the WMS-R, and patients with left mesial TLE performed worse than non-mesial left TLE patients [42]. However, although the test has been found to be reliable, multiple regression analysis revealed that the visual memory index was susceptible to a number of verbal influences [60]. This susceptibility suggests that right and left focus participants would not be easily distinguished. Left temporal focus participants perform worse than those with right temporal foci [64], but failures to find this difference between left TLE and right TLE groups on this task have also been reported [58]. Patients who were scheduled for right or left temporal focus removal could not be differentiated using this test [36]. The Logical Memory (Stories) Test of the WMS-R shows better performance by right TLE compared to left TLE participants [21], but left or right TLE, and left or right extratemporal participants are all impaired compared to controls [34]. However, other investigators could not detect a statistical

difference between right and left TLE participants [36; 46], or bilateral cases [57]. These findings and numerous others in the literature suggest that the widely used WMS-R frequently gives false lateralizing information [51] and as such is not a reliable test of epilepsy specific cognitive effects. Moreover, age and education levels act as confounds in this measure [67]. Thus, although the WMS-R is widely used, it appears to be ineffectual in analysis of epilepsy cases.

These results suggests that the use of another, less recognized measure of memory may be a superior alternative to the conventional WMS-R. Some alternative tests which have been shown to be effective for epilepsy identification are the least used in neuropsychological batteries, but even these tests show mixed results in their effectiveness. The Warrington Recognition Memory Test [WRMT; 68] has been found to be a good predictor of laterality in some studies[51], but in others the Recognition Memory Test for words and faces has been unable to differentiate generalized epilepsy participants from left or right TLE [12; 62]. The California Verbal Learning Test [CVLT; 22] shows that participants with prefrontal metabolic asymmetry ipsilateral to their TLE focus perform worse than those who do not have such asymmetry [46]. The CVLT has also been used to differentiate right and left TLE participants with inferior performance by left in some studies [42; 66], but it has also been found that laterality of TLE participants is not a significant predictor of CVLT performance [41]. Notably, the Visual–Verbal Test [31] and Maze Test [17] expose poorer performances in frontal lobe epilepsy compared to TLE participants [38], but no statement can be made on their effectiveness in differentiating the hemisphere that a partial epilepsy is located in. Although these memory tests have been somewhat successful in uncovering performance

differences in participants with epilepsy, the various contradictory findings makes the use of such tests in an epilepsy assessment battery a less than ideal solution.

Based on the reports here, it seems that a current epilepsy battery for memory should include the CVLT, the WRMT, the RCFT, and the Corsi Block Tapping Test. These have generally proven to be the most clinically useful for the analysis of location and severity of any epileptic activity and the inclusion of several tests should help to minimize error in diagnosis. However, there is certainly room for improvement in this battery, and perhaps a test that could perform the job of several of those above could streamline the neuropsychological battery currently used. The present study aimed to identify such a test.

This study presents a new test that could be used in place of a multitude of tests to effectively identify the cognitive deficits in memory of individuals with epilepsy from those without, and also identify the location of epilepsy activity in cases where it was isolated to one hemisphere. In this experimental design, visual versus verbal working memory was assessed using identical tasks with identical dependent variables. Reliance on visual versus verbal working memory was manipulated via the inclusion of secondary interference tasks designed specifically to tap one or the other processing stream. I hypothesized that individuals with left temporal lobe epilepsy would perform more slowly and less accurately than people with right temporal lobe epilepsy or controls on memory testing with a verbal distractor, and that right temporal lobe epileptics would perform more slowly and less accurately than left temporal lobe epileptics or controls on memory testing with a visual distractor. In addition, I hypothesized that individuals with generalized epilepsy, where epileptic activity occurs in both hemispheres, would do

poorly on both the memory task with visual and verbal distraction, likely at the level of the left and right temporal lobe epileptics in their respective deficit material. To examine these hypotheses and analyze the usefulness of this proposed test, the following study was undertaken.

METHODS

PARTICIPANTS

Two groups of participants were tested. One group was composed of patients with epilepsy and the other was age and education matched controls. Within the epilepsy group, participants were sub-classified as being left TLE, right TLE, and whole brain or generalized epilepsy patients. There was a final group with TLE in both hemispheres, or bihemispheric TLE. Group was determined by self report as well as viewing the participants' medical records to confirm their diagnosis and treatment regiment. Participants were volunteers drawn from the Edmonton Epilepsy Association, the Students with Disabilities Association of the University of Alberta, and the general population of the University of Alberta and the Edmonton community. All participants were briefed on the purpose of the experiment and were free to leave the experiment at any time if they so chose. Participants were also informed at the time of testing that they would be paid a nominal fee for their involvement. There were 41 participants in the study: 24 participants with epilepsy and 17 control participants. The different classifications of left focus epilepsy, right focus epilepsy, bihemispheric epilepsy and generalized epilepsy were composed of 8, 4, 5, and 7 participants respectively. The average age of participants with epilepsy and control participants was 38.99 (SE 2.36) and 39.53 (SE 2.55) respectively. The number of males in each group was 40% and 41.17% for epileptics and controls. The mean number of years of education was 15.5 (SE 0.68) for the epilepsy patients and 16.4 (SE 0.76) for controls. Twenty-five percent of the epileptics were left handed (much higher than the average of between 8 and 10% of left

handers in the general population) and only one (5.18%) of the controls was left handed. Despite this, left handed epileptic participants were not more prevalent in any one kind of epilepsy studied.

PROCEDURE

Testing occurred over two sessions of 1 hour each, in a well lit and quiet room. To determine overall IQ, participants completed the Wonderlic Personnel Test [WPT; 71], which has been found to approximate the revised Wechsler Adult Intelligence Scale [WAIS-R; 70] to within 10 IQ points in 90% of participants with epilepsy, with an administration time of only15 minutes [25]. The WPT consists of 50 multiple choice and short answer questions of verbal, mathematical, reasoning and spatial perception. Participants are required to complete as many of these, progressively more difficult, questions as they can in 12 minutes. Dodrill's estimation of the WAIS-R score for people with epilepsy required corrections based on age (above 38 years old + 7) and for sex differences in performance (male participants + 3) [25]. These adjustments were applied across all participants in the study. The control participants showed an average of 27, a 7 point advantage over the epilepsy patients without corrections. When only the epilepsy participants received the corrections, their average score became 26.79 which equates them with the controls. However, when similar correction is made on the control data their adjusted average is 32. Using a variation of the test developed by Buchanan, Pavlovic and Rovet [15] for working memory, immediate and delayed visuospatial working memory was tested (See Figure 1).

[illegible]

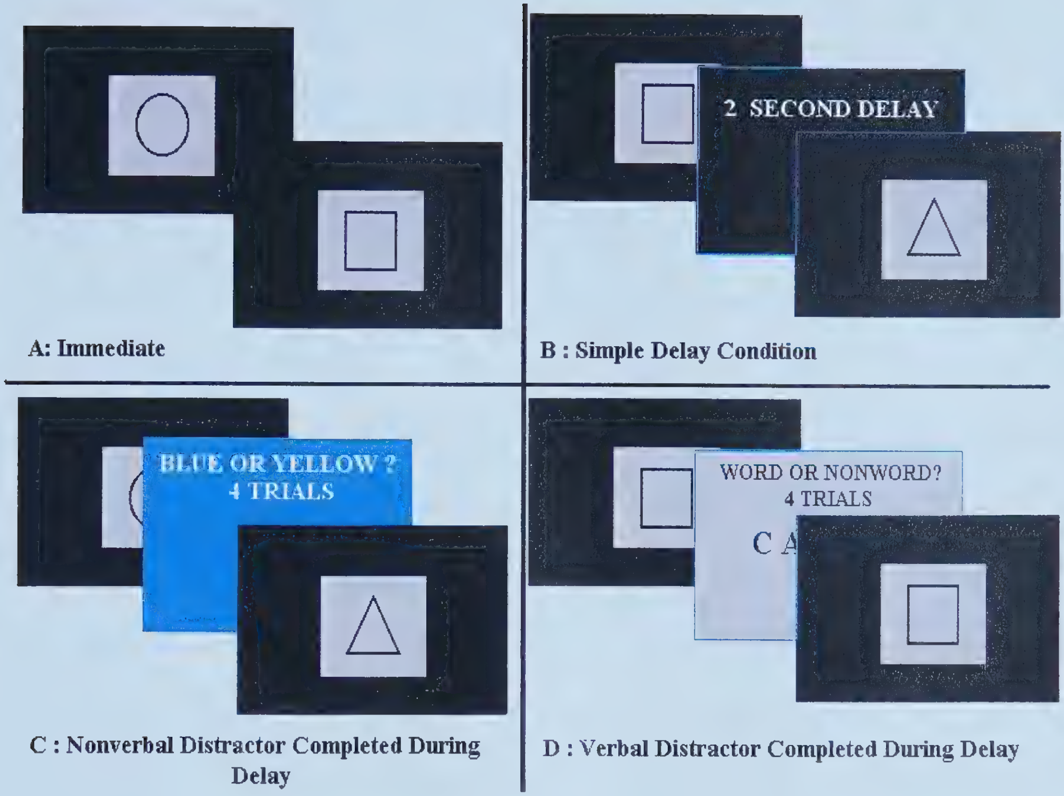

FIGURE 1: Sequence of visual arrays for the experimental procedure.
Sequence A examines participants' most basic memory processing of spatial information. Sequence B examines participants' working memory abilities. Sequence C examines visual working memory processing. Sequence D examines verbal working memory processing.

CONTROL CONDITIONS

Every participant completed each of the 4 conditions of the experiment. The first 2 conditions were control conditions. In the first condition, participants saw a geometric shape displayed in the centre of a grey screen with a black background displayed on a computer for 500 milliseconds. This was immediately followed by a second shape displayed in its place. Participants were asked to respond as quickly but accurately as possible as to whether the two shapes were identical, and did so by using 'Yes' or 'No' keys marked on the keyboard; 36 trials were completed by all participants. Participants were shown three example trials completed by the experimenter, and given additional exposure if needed. Error rates and reaction times served as the dependent measures. This experimental condition was used to determine the integrity of the most basic memory processing abilities of the participants and to serve as a baseline. A second condition introduced a 2 second delay between the first and second shape presentation to establish whether the participants had any encoding disorders, which would hamper their ability to maintain the image for 2 seconds. The same measures were taken from this test. The manipulations of interest occurred in third and fourth conditions.

TEST CONDITIONS

The participants then completed test phases of the experiment in which the delay consisted of two types of secondary tasks. In the third condition the secondary task was a colour recognition (is the screen blue?) where the screen would turn either blue or yellow, while in the forth condition the task was a lexical decision (is the letter string shown a real word?). Participants completed 4 of these decision tasks in each of the 36 trials of third and forth blocks of the experiment. These colour or word tests served as distractors to identify participants with deficits in visual or verbal working memory by a longer reaction time (RT) to the primary (shape decision) task and poorer accuracy scores. The RTs and errors in the immediate or baseline condition were examined to determine if there were any differences as a function of group membership. The predicted results of these experiments were that participants with left temporal lobe epilepsy would show longer reaction times than controls in the forth condition with word distractors, and that right temporal lobe epilepsy participants would show inferior performance to controls on the third condition with colour distractors. Generalized epilepsy participants, I hypothesized, would show a deficit in both these mediums compared to controls, and likely at the level of right and left temporal lobe epileptics in colour and word distractor trials, respectively. Predictions for the reaction times of the third and forth conditions are illustrated in Figure 2.

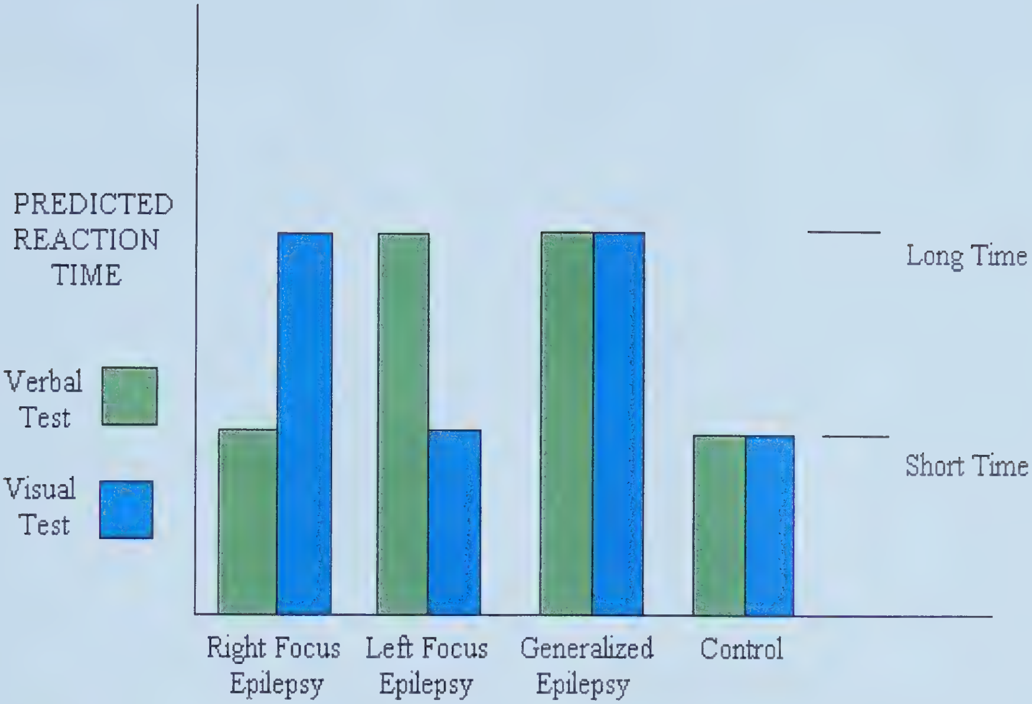

Figure 2: Predicted Differences in Working Memory of Subjects with Epilepsy

These predicted results are based on the well known isolation of verbal processing in the left hemisphere and visual processing in the right hemisphere in normal subjects. Poor reponse time results demonstrate damage to the centres responsible for these tasks in left and right focus subjects, as well as an overall effect on both in generalized epilepsy

The delay conditions of the RCFT and the RAVLT, which are two conventional tests of visual and verbal memory were examined for comparison with results from the experimental conditions. The RAVLT was used in place of the CVLT because this test was not available at the time of testing. The RAVLT was chosen as its replacement because similar to the CVLT, this test examines only verbal memory processing and its scoring is comparable to the RCFT.

The RCFT is a test of visuospatial construction ability and visuospatial memory, commonly used in neuropsychology to diagnose visuospatial deficits. The test was administered as follows. Participants were exposed to a figure composed of various geomet-

geometric shapes and were asked to copy the shape on a piece of paper. The elapsed time for completion of this copying task was recorded, and the experimenter made note of the order in which the participant drew the figure. Some participants may be unable to complete this task, so an initial judgement of the likeness of the picture indicates to the experimenter if the participant is capable of continuing or obviously has some greater deficit; no participants were incapable of continuing in this study. Participants then completed various distractor tasks, and after 3-5 minutes were required to draw the figure again from memory. Elapsed time and drawing order were recorded once again. After testing, the drawing was graded on accuracy to the original, based on a 36 point scale. Specific aspects of the drawing were marked on their correct placement and likeness to the original. The decline in the participant's score then becomes a representation of any potential memory deficits. Scoring of all drawings was completed by the experimenter then scored again by a colleague familiar with the procedure. Scores between reviewers were shown to be highly correlated (inter-rater correlation = .94) so an average of the two scores was taken. This measure of visual nonverbal memory was matched with its verbal counterpart, the RAVLT.

The RAVLT was used as a test of verbal learning and memory. A 15-item word list was read to the participants, and the participants were asked to say all the words from the list that could be remembered in any order. All the responses of the participants were recorded, including repeated words and confabulations. This process was repeated four times, with the same list of words, and all responses recorded. The participants were then read a different list of 15 words as a distractor, and asked to repeat back all the words that

could be remembered. Once this was complete, the participants attempted to say all the words from the original list (read five times) without prompts.

RESULTS

GENERALIZED VERSUS BIHEMISPHERIC ANALYSIS

Within the epilepsy group, there were a few participants who suffered from focal seizures in both hemispheres, or bihemispheric complex partial epilepsy. Several of the bihemispheric patients also suffered secondary generalized seizures, suggesting that they could be grouped with the generalized patients when examining seizure effects. On the advice of a neurologist and the assumption that generalized and bihemispheric patients suffer damage to both hemispheres, analysis was completed to confirm that the groups could be collapsed into a single category (See Table 1). A (2X4 - GROUP X TASK) MANOVA on RTs from conditions1-4 confirmed that there was no main effect of group, that is, there was no difference between bihemispheric and generalized participants, $F(1,10) = .000$, $p = .98$. Accuracy was also analysed in a GROUP X TASK MANOVA and again there were no differences between the generalized and bihemispheric epileptics, $F(1,10) = .303$, $p = .59$. Based on these results data from generalized and bihemispheric participants were collapsed into a common group of whole brain epileptics, and given the functional definition of generalized for the remainder of this paper.

TABLE 1 : Comparison of average reaction time in milliseconds and accuracy for generalized and bihemispheric epilepsy groups (with standard error)

	COND. 1	COND. 2	COND. 3	COND. 4
	Reaction Time	**Reaction Time**	**Reaction Time**	**Reaction Time**
Generalized	703 ms (66.1)	689 ms (50.3)	1644 ms (533)	1413 ms (534)
Bihemispheric	961 ms (215)	844 ms (143)	1405 ms (136)	1283 ms (137)
Average	826 ms (98.1)	753 ms (66.4)	1544 ms (307)	1359 ms (268)
	Accuracy	**Accuracy**	**Accuracy**	**Accuracy**
Generalized	0.99 (0.00)	0.98 (0.01)	0.74 (0.09)	0.85 (0.05)
Bihemispheric	0.97 (0.03)	0.93 (0.06)	0.72 (0.08)	0.85 (0.06)
Average	0.98 (0.01)	0.96 (0.03)	0.73 (0.06)	0.85 (0.04)

Note. COND. = Condition
Generalized = generalized epilepsy group
Bihemispheric = bihemispheric complex partial epilepsy group

CONDITION 1 : NO DELAY MEMORY TASK

The first experimental condition – where there was no delay – was intended to act as a baseline measure (See Table 2). To determine that there were no group effects in this condition a 4 way between participant ANOVA was conducted on RTs: $F\ (3,37) = .45$, $p = .72$, p >.10 and on accuracy: $F\ (3,37) = .31$, $p = .82$. The analyses demonstrated that there were no differences as a function of group membership on this baseline task and therefore justify the use of it in the following subtractive analyses in which the individual's baseline RTs were subtracted from his or her trial RTs to control for individual RT variability. Put simply this baseline RT was subtracted from the mean RT of participants in conditions 2, 3, and 4, to provide a subtracted reaction time (SRT) assumed to capture working memory processes.

TABLE 2 : Comparison of condition 1 reaction time in milliseconds and accuracy by group average (with standard error)

Group	AVG. RT	AVG. ACC.
Left	735 ms (62.2)	0.99 (0.01)
Right	723 ms (52)	0.97 (0.02)
Generalized	826 ms (97.9)	0.98 (0.01)
Control	727 ms (50.4)	0.98 (0.01)
Overall	757 ms (37.5)	0.98 (0.01)

Note. AVG. RT = Average Reaction Time
AVG. ACC. = Average Accuracy

CONDITION 2 : DELAYED MEMORY TASK

The second experimental condition contained a delay that was not filled with distractor tasks. This condition was included to further test the integrity of simple memory stores by increasing the difficulty of the task, but was not expected to show group effects given that it was assumed that epilepsy has its effect in higher order memory requirements (See Table 3). A 4 way MANOVA was conducted on the RT data, the SRT data and the accuracy. There were no significant effects of group in these analyses with $F(3,37)<1$ in all cases. The results of this task demonstrate that the epileptic participants could perform very simple spatial memory tasks at a level equal to their matched controls.

TABLE 3 : Comparison of condition 2 reaction time in milliseconds and accuracy by group average (with standard error)

Group	AVG. RT	AVG. ACC.
Left	743 ms (114)	0.96 (0.02)
Right	693 ms (99)	0.99 (0.02)
Generalized	753 ms (66.4)	0.96 (0.03)
Control	791 ms (121)	0.96 (0.02)
Overall Average	761 ms (57.8)	0.96 (0.01)

Note. AVG. RT = Average Reaction Time
AVG. ACC. = Average Accuracy

CONDITION 3 AND CONDITION 4 : NONVERBAL AND VERBAL DISTRACTORS

The two experimental conditions of primary interest in this study were the ones containing the distractor tasks (See Table 4). The first analysis on data from these tasks was a simple 2X2 (GROUP X TASK) MANOVA where group membership was defined by the presence or absence of seizures (i.e. contrasts of all epileptics with controls). Both the SRT data (F (1, 39) = 5.75, p = .02) and the accuracy data (F (1,39) = 9.86, p = .003) produced a significant main effect of group, with a clear deficit in performance by the epileptics versus controls.

Complementary analyses were conducted on the data from the two standardized counterparts to these experimental conditions (See Table 5). The standardized scores from the RCFT and the RVLT were entered in a 2X2 (GROUP X TASK) MANOVA where group membership was defined by the presence or absence of seizures and task was defined as the visual versus verbal scores. As Table 5 indicates, there was a main effect of group (F1,39)=23.19, p<.005) with the epileptic group performing far below the controls. As in the experimental tasks there was no main effect or interaction of the visual versus verbal manipulation (F<1).

To examine this ability of the test to distinguish between different types of epilepsy, the SRT and the accuracy data were entered into 4X2 (GROUP X TASK) MANOVAs where group was defined by right, left or generalized epilepsy or controls and task was the visual and the verbal distractor conditions. Analysis of group differences in SRT scores for condition 3 and condition 4 revealed an effect approaching significance, F (3,37) = 2.46, p = .08. Based on the hypothesis, LSD planned comparison further showed that control participants did better than the generalized epileptic participants on condition

3, $p = 0.01$. The same analysis on the accuracy data revealed a significant group difference, $F = 3.44$, $p = .03$, with controls performing marginally better than all three epilepsy groups but only significantly better than the generalized epileptics, $p = .004$. No planned comparisons involving the right or left hemisphere epileptics were significant: Neither the SRTs ($F(1, 8) < 1$) from the right versus left groups from condition 3 and condition 4 (2 x 2 MANOVA) nor the accuracy $F(1, 8) <1$ demonstrated main effect of group or task.

Complementary analyses were conducted on the standardized counterparts to the above two conditions. The standardized scores from the RCFT and the RAVLT were subjected to a 4X2 (GROUP X TASK) MANOVA where group was defined by right, left or generalized epilepsy or controls and task was the visual and the verbal delay conditions of these tasks. As the mean scores in Table 5 indicate, there was a main effect of group membership ($F(3,37) = 10.59$, $p<.005$) and LSD planned comparisons (at $p <.05$) indicated that the right hemisphere group performed more poorly than either of the other epilepsy groups and the controls. Typical results on the RCFT immediate recall from participants in all four groups can be seen in Appendix I. These figures provide an indication of the kind of deficit demonstrated in this study. The left and generalized groups performed more poorly than the controls but did not differ from each other. In this analysis as in the previous one involving experimental conditions there were no main effects or interactions with task ($F<1$).

[illegible]

TABLE 4: Comparison between all groups across condition 3 and condition 4 by average (with standard error)

Group	SRT 3	Acc. 3	SRT 4	Acc. 4
Left	343 ms (66.8)	0.85 (0.03)	377 ms (164)	0.81 (0.02)
Right	608 ms (393)	0.83 (0.09)	473 ms (225)	0.79 (0.07)
Generalized	719 ms (285)	0.73 (0.06)	533 ms (298)	0.85 (0.04)
Combined Epileptics	**575 ms (157)**	**0.79 (0.04)**	**471 ms (159)**	**0.83 (0.02)**
Control	**177 ms (70.8)**	**0.91 (0.01)**	**187 ms (80.5)**	**0.90 (0.03)**

Note. SRT 3 = Subtracted Reaction Time for Condition 3
Acc. 3 = Accuracy for Condition 3
SRT 4 = Subtracted Reaction Time for Condition 4
Acc. 4 = Accuracy for Condition 4

TABLE 5: Comparison between all groups across conventional memory tests by average (with standard error)

Group	RCFT	RAVLT
Left	14 (2.6)	11 (0.99)
Right	7 (1.9)	8 (2.2)
Generalized	15 (1.8)	10 (0.84)
Combined Epileptics	**14 (1.4)**	**10 (0.63)**
Control	**21 (1.8)**	**14 (0.44)**

Note. RCFT = Score for RCFT Immediate recall after distractor (RCFT-Immediate)
RAVLT = Score for RAVLT recall after distractor (Trial 6)

To determine whether these standardized tasks truly are counterparts to the experimental conditions, correlations were conducted between the experimental conditions and the traditional test measures which most closely match them. The correlation values found in Table 6 (with df = 40, $p<.05 = .30$) show that there is a significant correlation between the experimental tasks and their standardized counterparts, except for the non-significant correlation of the verbal SRT with the RAVLT measure of recall after distraction.

Table 6: Correlation of standard and experimental tasks of verbal and visual performance

Variables	R value	Variables	R value
Verbal task SRT and RAVLT	-0.03	Verbal task ACC and RAVLT	0.32
Colour task SRT and RCFT	-0.30	Colour task ACC and RCFT	0.38

Note. SRT = Subtracted Reaction Time ACC = Accuracy
RCFT = RCFT Immediate recall after distractor (RCFT-Immediate)
RAVLT = RAVLT recall after distractor (Trial 6)

In addition, specific epilepsy variables were correlated using only the data from the epilepsy population (N = 24), to investigate any within group correlations that would be hidden or increased when including control participants. Appendix II contains the relevant correlations. With alpha set at .05, there was a negative correlation between the RAVLT Trial 6 score (performance after distraction) and the number of medications taken by epileptics. All other epilepsy specific variables could not be predicted by the scores on this set of tests.

DISCUSSION

This experiment had two primary research objectives. The first was to distinguish epileptics from controls using a redeveloped test of visuospatial working memory with visual and verbal distractors. MANOVA analyses comparing control participants to those with epilepsy did show a difference in their performance, as hypothesized. Hence this objective was achieved. Epileptic participants appear to perform worse on the two tasks with distractors but particularly on the colour distractor task. Generalized epileptics performed comparatively worse than all other groups. Although not all the experimental effects reached statistical significance, it seems clear from these data that generalized epileptics are disadvantaged compared to other kinds of epileptics in some aspects of verbal and visual memory.

The second research objective of this study was to distinguish between participants with different kinds of epilepsy based in their results. Recall the projected outcome in Figure 2 where it was hypothesized the contrast between visual and verbal distractor conditions would reveal a dichotomy with right focal participants and generalized participants performing poorly on the visual distractor task, and left and generalized participants performing poorly in verbal distractor task. The MANOVA analyses comparing the different kinds of epilepsy did not reveal this expected pattern. This failure may be due to a number of confounds within the experimental design and recruitment process. First and foremost, the sample size of the different kinds of epilepsy, especially right hemisphere focal patients, was likely inadequate to provide the kind of statistical strength necessary for the analysis. Although there were a sufficient number of generalized participants, the other two subgroups were quite small and made any between

group comparisons difficult. Given these small numbers the trends in the data suggest that the underlying hypothesis may be correct and support the need for a larger study. Right focal participants did much worse (SRT = 608) than left (SRT = 343) or controls (SRT = 177) on the colour distractor task, and the difference between their colour and word scores was noticeable. Moreover, contrasts of the data from the left focal group (accuracy = 0.81) with controls (accuracy = 0.90) on the verbal distractor task nearly reached significance (p = .075). Thus, although there was numerical support for the hypothesis a larger sample size is required to provide the necessary power to demonstrate a between epilepsy type effect[1].

The trends in the data from the experimental tasks provide insight into the extent of working memory impairments in epilepsy: Left hemisphere patients performed the best, generalized performed the worst, and right hemisphere group fell between these two groups. The question that then arises is why did generalized epileptics perform worse than focal right epileptics on colour testing, and much worse than left focal patients. Theory on hemispheric specialization would suggest that the right focal patients would perform as poorly if not worse than generalized epileptics. As well, complex partial epilepsy, especially mesial temporal lobe epilepsy, is more frequently associated with memory problems than generalized, if the effects of medications are accounted for [42]. It may be that generalized epilepsy has a more severe effect on the memory systems, as seizure activity can extend from the thalamus though the entire neocortex, compared to focal epilepsy which centres epileptic spikes around few particular foci. Yet the present result is not completely surprising, as several authors have noted an inability of neuropsychological memory tests to differentiate between right temporal and left

[1] The sample size for the study was calculated based on the Buchanan et al. (15) study of Turner Syndrome

temporal epilepsy [41; 46; 65], or even generalized epilepsy [58; 62]. In this sense, the completion of the first objective of the experiment may be a significant step towards development of a truly effective neuropsychological battery for epilepsy, as this test has moved towards the isolation of epilepsy through neuropsychological means, which has in the past --as seen in the review-- been rather elusive to several of the widely used neuropsychology tests. It is important to also note that the research yielded a secondary benefit of identifying where in the memory system the deficits occur in epileptics.

Epileptics could not be distinguished from controls on either condition 1 or condition 2. Their normal performance on condition 1 was not surprising, because this task contains a minimal memory component, depending on the sensory register. It was more surprising, and informative, to note that they did not perform worse than controls on the simple delay condition. The unimpaired performance of epileptics in condition 2 suggests that individuals with epilepsy do not have a deficit in the initial encoding stage of working memory because such a deficit would have resulted in poorer performance in this task. The aspect of working memory that appears to be implicated in the cognitive profile of epileptics is the management of multiple pieces of information or the of use rehearsal strategies while completing other tasks. Epileptics may absorb information correctly, but then discard a great deal of it when exposed to other input, due to the large cognitive load. Thus, the contrast between spared memory in condition 2 and impaired memory in conditions 3 and 4 helps to pinpoint the deficit in working memory that is broadly demonstrated in such tasks as the RCFT, the CVLT and the Corsi Block Tapping Test. This pinpointed deficit is likely the juggling or maintenance of multiple and unrelated

pieces of information during short-term recall, where the central executive is unable to cope with the demands of the tasks.

FUTURE RESEARCH DIRECTIONS

Maintaining multiple pieces of information may be more difficult for individuals who suffer from interictal activity [43]. In fact, it has been shown that it is possible to test for TCI in epilepsy patients, by using tasks which force the participant to extend to the limits of their cognitive capacity [43]. The most effective tests for such detection have been found to be short term memory tasks, information processing tasks, and forced choice reaction time [1; 10; 43]. Thus, it is possible that the tasks used in this paper are tapping some of the processes most directly compromised, not by epilepsy per se, but by the TCI some epileptics experience.

Individuals who suffer from TCI are able to maintain information provided to them in normal circumstances but distraction causes a large increase in the level of memory loss [43]. Interestingly, TCI spikes are associated with *increased* reading speed but decresed accuracy in school children [49]. Thus, the deficit specifically related to TCI may be more evident in accuracy rates rather than in reaction times. This may explain why the word distractor task in the current study did not show a larger effect in reaction time than accuracy. Although the individuals who were part of this study may not all be suffering from TCI, and the examination of TCI effects was not an original goal of the study, it may be that the tasks revealed the presence of interictal spikes and their resulting impairment of higher order cognitive ability.

TCI is most often noted in patients with generalized epilepsy, especially tonic clonic seizures [14]. Further investigation of the medical records of the people with epilepsy in this study revealed that of the participants in group 3 (generalized) 11 of 12 (92%) showed spike and wave, disrhythmia, or rhythmic activity during electroencephalogram (EEG) testing with no external signs of seizure, compared to 8 from the left and right focal groups combined (67%). The information from these medical records is obviously not a clear indication that the patients were experiencing TCI during testing. However, the record of this activity in the past suggests at least some likelihood of such activity during the testing session. In addition to the generalized group, 3 epileptics with TCI were drawn from the right focal group (75%) and 5 were drawn form the left group (71 %). Although there is insufficient data to run formal analyses on TCI effects, the accuracy on condition 3 shows at least a numerical trend in the direction that would be predicted if TCI was involved: The generalized group being the most inaccurate and the left focal group being the best. Thus this pattern is consistent with the notion that interictal activity may be involved in impairments on these tasks.

There were too few participants without suspected TCI to do a formal analysis of the differences due to this factor. However, a superficial examination of the possible effect of potential interictal activity on the test results was completed and the data appear in Table 7. Data from the standardized tests and the two delay conditions were evaluated for individuals with irregularities in their EEG versus individuals without. These data show numerical differences between the two groups, favouring the group without TCI in every test except the RCFT and the colour distractor accuracy. When looking at the reaction time to the distractor tasks (colours and words), the average reaction time of the

participants with EEG abnormalities was also 200 milliseconds slower than that of the epilepsy participants without such abnormalities, and controls were found to perform only 10-20 milliseconds faster than epileptics without EEG abnormalities. Thus the experimental test may provide a two stage approach to identify the existence of epilepsy in a participants, and the possibility of interictal activity, based on reaction time and accuracy scores that take approximately 30 minutes to complete, compared to the 3 or 4 hour time periods associated with most neuropsychological batteries. Of course it would be unwise to suggest that the proposed test should be implemented as a measure simply based on this small and short study, but it does provide evidence that repetition with a larger population could produce solid evidence that this test does in fact tap into the effects of interictal activity. Given how controversial many of the discussed tests are in their ability to isolate different kinds of epilepsy, a test that could potentially identify those individuals who were constantly experiencing epileptic activity from those who were not would be invaluable in the diagnosis and treatment of interictal activity.

TABLE 7 : Test scores of epilepsy participants with and without EEG abnormalities (with standard error)

Abnormal EEG	RAVLT -Trial 6	RCFT – Immed.	SRT 4 (words)	Accuracy 4	SRT 3 (colours)	Accuracy 3
NO	11.6 (1.12)	13.1 (3.53)	400 ms (213)	0.84 (0.05)	514 ms (292)	0.77 (0.08)
YES	9.63 (0.73)	13.45 (1.56)	490 ms (195)	0.82 (0.03)	591 ms (186)	0.79 (0.04)

Note. Abnormal EEG is suggested to be associated with transient cognitive impairment (TCI)

The detection of interictal activity is of equal clinical importance as the detection of epilepsy. TCIs in some children may be so frequent that they can impact both social skills

and academic performance significantly [10]. Extensive monitoring of spike and wave activity in paediatric neurology patients has shown that parents, teachers and other caregivers often underestimate the number of interictal events by a factor of 10 to as much as 100, and collectively thousands of interictal events may occur for a span of several hours of the day [9]. These interictal events can be recorded by a spike-and-wave detector which measures all the ictal activity [8]. Early detection of such activity can allow drug treatment to begin early, and likely reverse some of the effects of the interictal discharges. Besag [10] suggests that nocturnal interictal discharges, and overt EEG abnormality may be the root cause of decline in I.Q. seen in many cases of children with epilepsy[10, pg 267]. Therefore the development of an effective and non-invasive test to provide evidence of interictal activity in epilepsy patients would be an important contribution to the ongoing treatment of people with epilepsy, and this test is submitted as a candidate for further investigation.

CONCLUSIONS

The literature on the cognitive examination of epilepsy has many tests, with varying effectiveness. Current cognitive tests used for epilepsy are not entirely sensitive to the particular characteristics of this disorder. Of the 87 tests reviewed by Cochrane et al. [19], only 20 were found to show statistically significant cognitive effects in epileptic participants. Testing must be more sensitive than this. What is more surprising is that very few clinicians administer the batteries specifically developed for epilepsy. This demonstrates the lack of uniform treatment of patients with epilepsy, as well as the lack of attention to effects other than those caused by medications. Many people with epilepsy experience ongoing cognitive effects that reach beyond the time when seizures occur and the post-seizure confusion that can follow them. These conditions must be more widely acknowledged, and efforts must be made to isolate this effect and provide ways to help people with epilepsy cope with this condition. The development of a more effective neuropsychological test for epilepsy, like the one proposed above, should be a top priority for researchers and clinicians alike [18]. The pursuit of a better standard of living for people with epilepsy should be just as important as the noble pursuit for its cure.

The aim of the present study was to use cognitive experimental testing to determine if there is a better and more reliable behavioural test to identify epilepsy in patients, and determine location of focal epilepsy activity. This would have the obvious advantages of streamlining neuropsychological patient testing, and providing a clinical tool that is more easily interpreted and understood. This first objective was achieved, as participants with epilepsy were found to perform significantly worse than control participants, and epileptics with ictal activity in both hemispheres were shown to perform worse than left focus,

right focus and control participants. Secondly, this study aimed to identify different kinds of epilepsy within epileptic samples, specifically differentiating right focus epileptics from left focus epileptics. Although this objective was not completed, a secondary finding suggested that perhaps this test is sensitive to interictal activity in people with epilepsy. Successful identification of such deficits would serve to assist future epilepsy participants by indicating a need for specialized assistance in school or working environments for those with interictal activity. This assistance could provide a greater level of achievement for these individuals and allow them to play a more integral role in industry and society.

With the above goals in mind, the important findings from the present study were that the test can distinguish epileptic participants from controls and that poorer performance by generalized participants compared to controls was seen consistently. The study was unable to distinguish between right and left temporal epileptics. The need for future research and confirmation using reliable spike and wave detection systems is clearly indicated, and repetition with larger sample sizes is also required.

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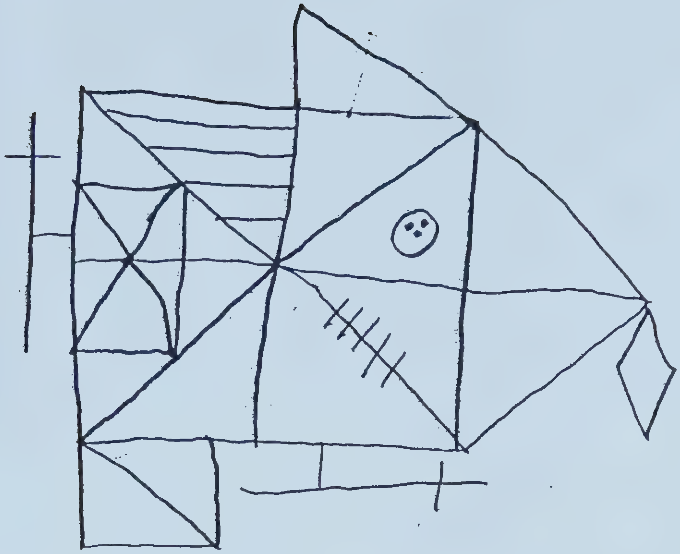
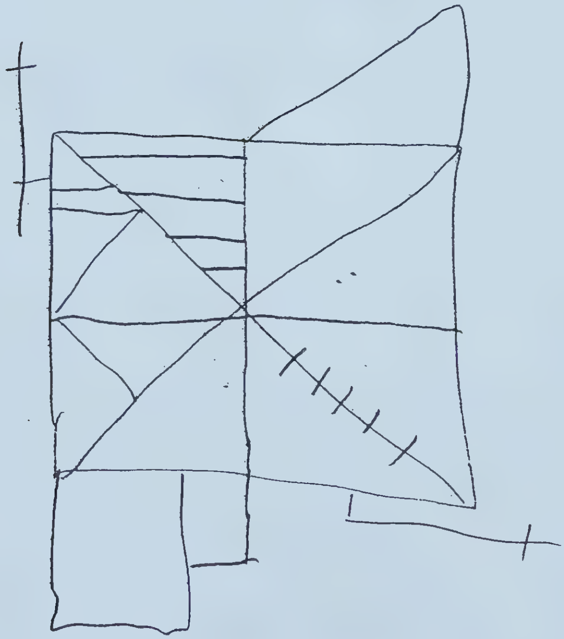
APPENDIX I

EXAMPLES OF PARTICIPANT RCFT PERFORMANCE

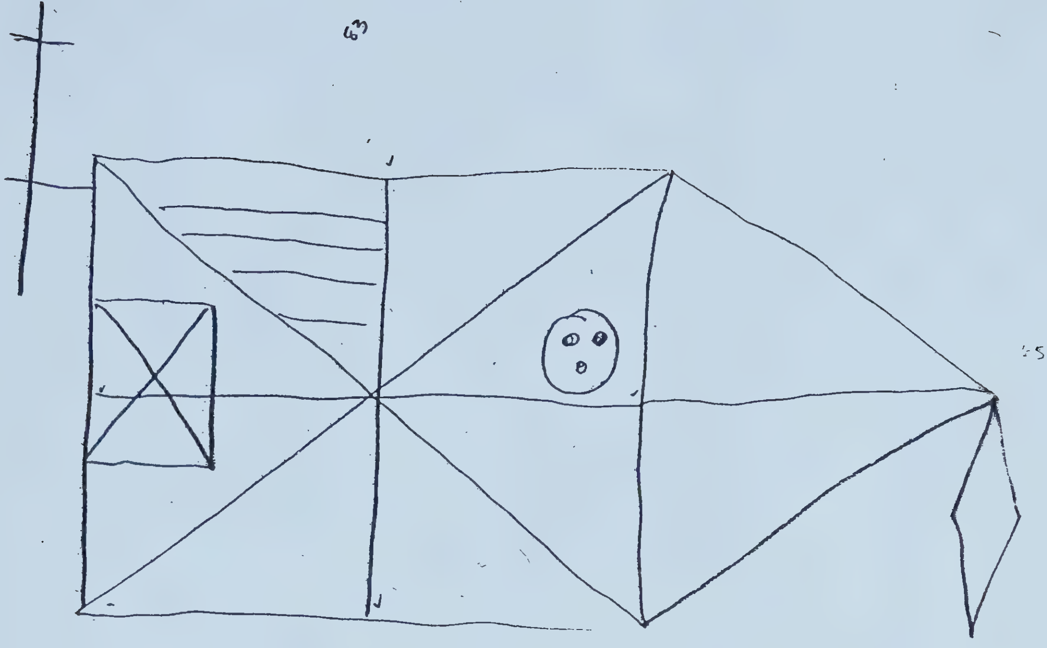


HIGH SCORE

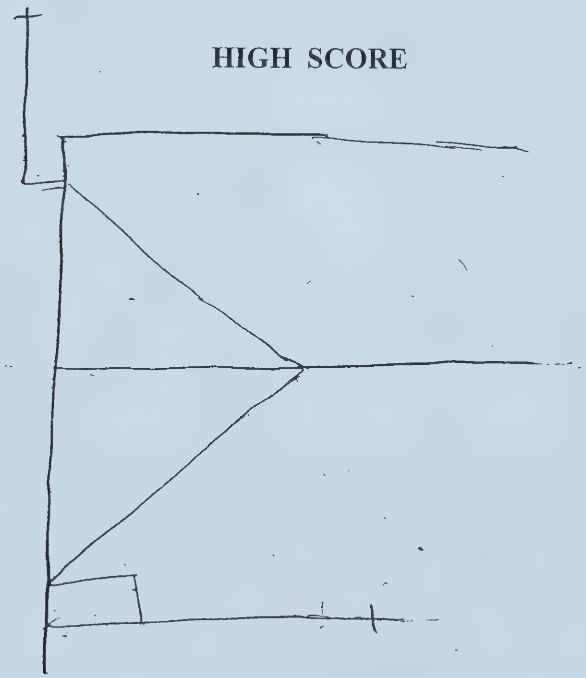


LOW SCORE

FIGURE 3 : Examples of control participant RCFT performance

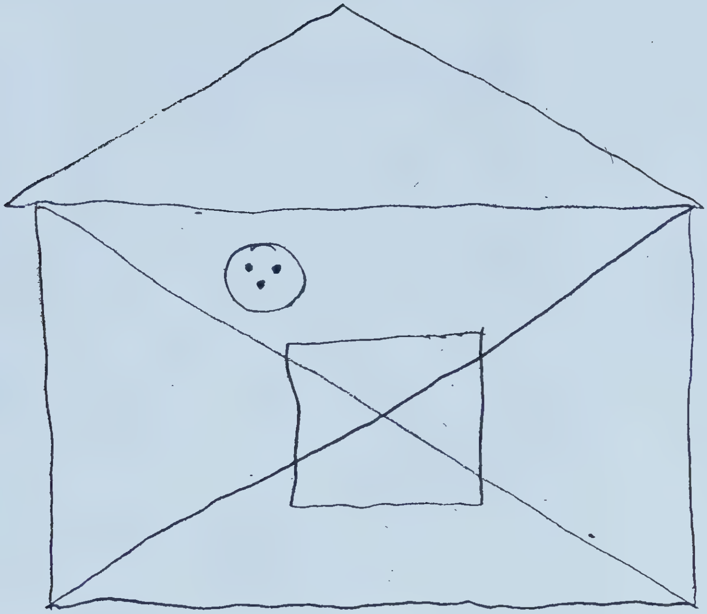


HIGH SCORE

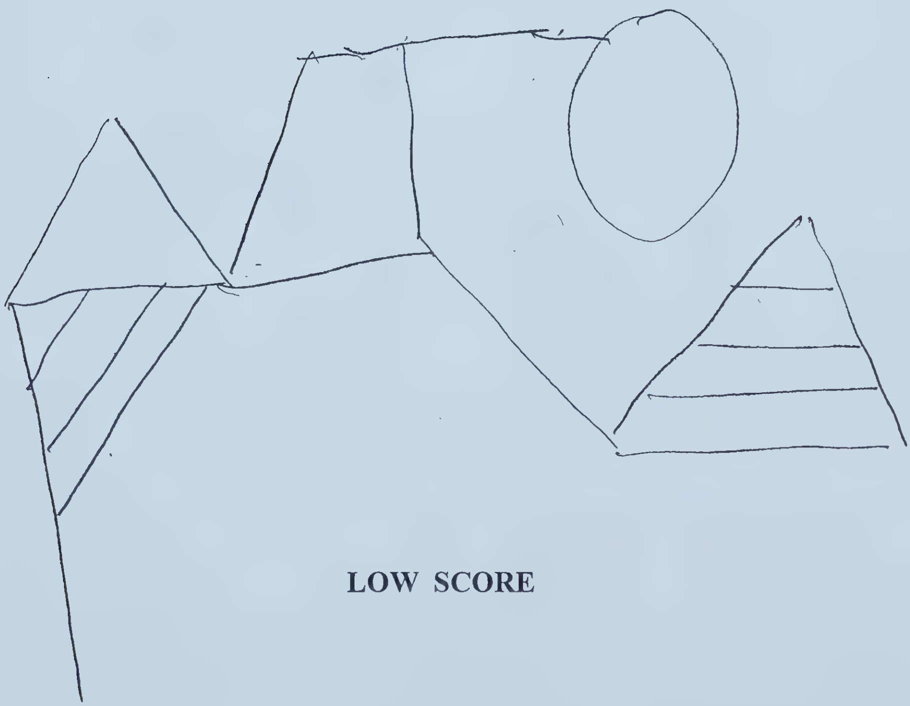


LOW SCORE

FIGURE 4 : Examples of left focus participant RCFT performance

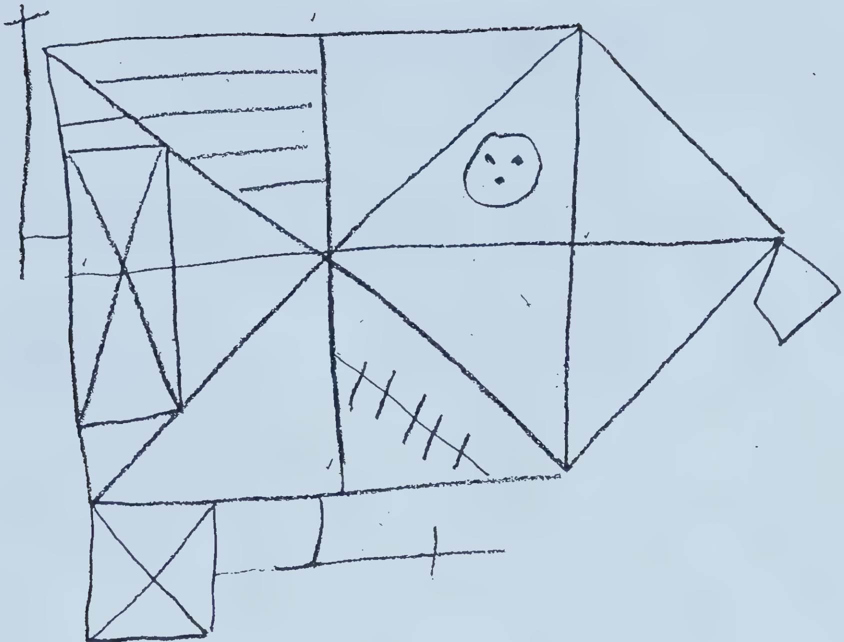


HIGH SCORE

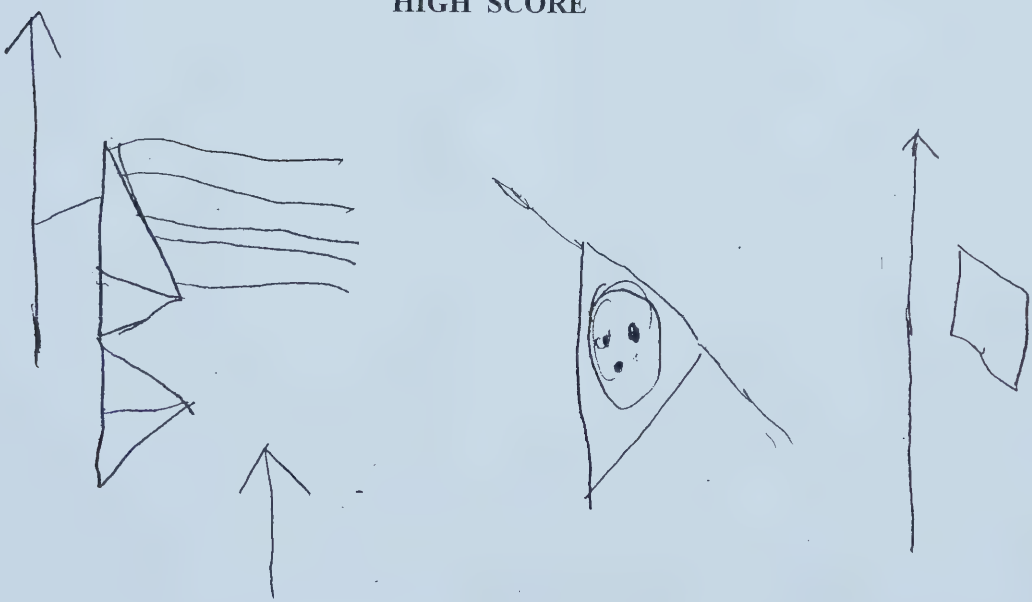


LOW SCORE

FIGURE 5 : Examples of right focus participant RCFT performance



HIGH SCORE



LOW SCORE

FIGURE 6 : Examples of generalized participant RCFT performance

APPENDIX II

TABLE 8 : Correlation of relevant epilepsy factors with test scores

	SRT-3	Accuracy 3	SRT-4	Accuracy 4	RCFT - Immediate	RAVLT Trial 6
#Meds	.20	.17	-.33	.09	.16	**-.52**
Age of on-set	-.32	.20	-.20	.19	-.11	-.05
Seizure Frequency	.20	.17	-.04	.05	-.01	.16
Time since last seizure	-.35	-.21	.34	-.11	-.09	.27